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Original Articles

Short-course moxifloxacin therapy for treatment of acute bacterial exacerbations of chronic bronchitis

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Chronic bronchitis is common among adults and infectious exacerbations contribute considerably to morbidity and mortality. We aimed to compare the safety and efficacy of moxifloxacin to clarithromycin for the treatment of patients with acute bacterial exacerbations of chronic bronchitis (ABECB) using a prospective, randomized, double-blind, parallel group trial.

Between November 21, 1996 and April 7, 1998, 936 patients with acute exacerbations of chronic bronchitis (AECB) were enrolled at 56 centers across the United States of which 491 (52%) had ABECB (i.e. pretherapy pathogen).

Patients were randomized to either oral moxifloxacin 400 mg administer once daily, for either 5 or 10 days, or clarithromycin 500 mg bid for 10 days. For the purpose of study blinding, the patients taking moxifloxacin received placebo to maintain uniform dosing.

The main outcome measures were bacteriological response at the end of therapy (post-therapy days 0–6) and follow-up (7–17 days post-therapy) visits, as well as overall clinical response, clinical response at the end of therapy and clinical response at follow-up. Two patient populations were analyzed: efficacy-valid (i.e., those with a pretherapy pathogen) and intent-to-treat (i.e., all subjects that took drug).

In 420 efficacy valid patients with a pretherapy organism, overall clinical resolution was 89% for 5 days moxifloxacin *vs.* 91% for 10 day moxifloxacin *vs.* 91% for 10 day clarithromycin. Bacteriological eradication rates at the end of therapy were 94% and 95% for 5-day moxifloxacin and 10-day moxifloxacin, respectively, and 91% for the clarithromycin group. Eradication rates at follow-up were 89% and 91% for 5-day moxifloxacin and 10-day moxifloxacin respectively, and 85% for the clarithromycin group. Among 926 intent-to-treat patients (312 5-day moxifloxacin, 302 10-day moxifloxacin and 312 clarithromycin), drug-related events were reported for 26%, 30% and 35%, respectively.

Moxifloxacin 400 mg once daily, as a 5 or 10 day regimen, was found to be clinically and bacteriologically equivalent to 10 day clarithromycin for the treatment of ABECB. Given its favorable safety and tolerability profile, moxifloxacin administered once daily for 5 days may be as effective and a more convenient treatment than a standard course of clarithromycin for patients with ABECB.

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Introduction

Almost one in four adult Americans experience symptoms of chronic bronchitis (1,2), accounting for approximately 12 million physician visits annually, at a cost of more than $300 million per year (3). Acute exacerbations of chronic bronchitis (AECB) are a frequent complication of this condition and are often precipitated by environmental agents (e.g. air pollution, smoking), allergy, alcohol consumption, secretion clearance problems, acute viral respiratory infections, or decreases of pulmonary medications (4,5). Infection, identified by significant numbers of bacteria, is the etiology in approximately 50–60% of AECB episodes (4,5,6). While some patients may resolve their bacterial infection without anti-microbial therapy, their illness can be protracted and may require hospitalization following the development of pneumonia and respiratory insufficiency. Accordingly, patients with acute bacterial

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exacerbations of chronic bronchitis (ABECB) who present with increased dyspnea, cough, purulent sputum production and evidence of bacterial infection can benefit from anitbacterial therapy (4,5). Unfortunately, the decision to initiate antimicrobial therapy can be difficult because symptoms associated with ABECB are indistinguishable from those associated with acute exacerbations due to non-bacterial etiologies (5). In a recent meta-analysis, a small benefit to antibiotics over placebo in treatment of unspecified AECB was documented, as well as evidence that peak flow measurements improved significantly in antibiotic-treated patients (8).

The pathogens most commonly associated with ABECB have been *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*, with *Haemophilus parainfluenzae* appearing more frequently in recent years (4,5,9). Over the past decade, the levels of resistance to frequently prescribed antibiotics among these pathogens have risen significantly. In the U.S., almost every clinical isolate of *M. catarrhalis* produces β-lactamase, approximately 40% of *H. influenzae* isolates are β-lactamase producers and resistant strains of *S. pneumoniae* resistant to β-lactams and macrolides have been increasing worldwide (10,11,12). By the year 2000, it has been estimated that approximately 50% of *H. influenzae* isolates will produce β-lactamase (10). Accordingly, efforts to combat bacterial resistance have focused on the development of new antimicrobials with broader spectra of activity with less indication to develop resistance. Physicians should consider the local patterns of resistance when selecting an antibiotic for treatment of ABECB, as many older agents, such as amoxicillin and trimethoprim/sulfamethoxazole, may no longer be effective.

Moxifloxacin in a new 8-methoxyquinolone with excellent *in vitro* activity against commonly encountered Gram-positive and Gram-negative respiratory tract pathogens (13,14). It has excellent *in vitro* activity against pneumococcal strains resistant to β-lactam and macrolide antibiotics and good activity against atypical respiratory tract pathogens (13,15,16). Against *S. pneumoniae*, the MIC_{90} for moxifloxacin is 0.25 mg l^{-1}, which is at least four to eight-fold more active than ciprofloxacin and levofloxacin and at least as active as trovafloxacin (13). Moxifloxacin has reported MIC values of 0·06 μg ml^{-1} for both *H. influenzae* and *M. catarrhalis* (13). Importantly, β-lactamase activity or macrolide resistance mechanisms do not influence the *in vitro* activity of moxifloxacin.

Based on moxifloxacin's *in vitro* activity against respiratory pathogens and its pharmacokinetic profile (17,18), a dose of 400 mg once daily should provide serum levels for adequate bactericidal activity for patients with ABECB. Hence, the purpose of the current study was to assess the bacteriological efficacy and safety, as well as compare the clinical efficacy, of treatment with moxifloxacin (400 mg once daily) for 5 or 10 days with that of clarithromycin (500 mg twice daily) for 10 days in patients with ABECB. The once daily administration schedule and option of a shorter, 5-day course of therapy with moxifloxacin may have compliance advantages over existing therapies. Although this study was undertaken, in part, to satisfy registration requirements for the licensing of new drugs, the primary population for analysis for this manuscript was patients with documented pretherapy bacterial etiologies. We chose to focus our analyses on those patients with a documented bacterial infection since this subgroup should best determine the effectiveness of any antimicrobial.

Methods

STUDY DESIGN

This was a double-blind, randomized, active controlled, parallel-group trial designed to compare moxifloxacin, using a 5-day and 10-day regimen, to 10 day clarithromycin, in the treatment of ABECB. Patients were enrolled at clinical sites randomly distributed throughout North America. These sites were clinic-based and managed by physicians who included primary care physicians, pulmonologists and infectious disease specialists. The trial format was conducted according to the guidelines described by the Committee on the Consolidation of Standards for Reporting Trials (19).

STUDY POPULATION

Patients eligible for inclusion in the study were 18 years or older with underlying chronic bronchitis as defined by the daily production of sputum on most days for at least 3 consecutive months for more than 2 consecutive years and who had an AECB clinically thought to be caused by a bacterial pathogen. Patients with a diagnosis of chronic obstructive pulmonary disease (COPD) were also accepted. Patients with mild to moderate respiratory exacerbations were entered into the study and categorized as Types I, II, and III [as defined by the American Thoracic Society (2) and Anthonisen et al. (5)]. The acute nature of the infection was documented by recent increases of bronchopulmonary symptoms and laboratory evidence of lower respiratory tract bacterial infection. In order to be eligible for study participation, the patient must have had increased purulent/mucopurulent sputum and at least one of the following: increased cough, increased dyspnea, increase of sputum volume, or presence of fever (oral temperature $>100{\cdot}4^{\circ}$F or 38°C).

Patients were excluded for the following reasons: allergy or severe adverse reactions to carboxyquinolone derivatives or macrolide derivatives; pregnancy or lactating; history of severe cardiac failure [class IV of the New York Heart Association (NYHA) classification]; severe respiratory tract infections requiring parenteral antimicrobial therapy or mechanical ventilatory support; chest X-ray suggestive of a new pneumonia; evidence of significant liver or renal impairment; or needed a concomitant antibacterial agent with a spectrum of activity similar to the study drugs. Prospective patients were also excluded if they received drugs known to affect QT interval (e.g. terfenadine, astemizole, etc.); or received previous therapy with a systemic antibiotic for more than 24 h prior to enrollment. Adjunctive medications such as bronchodilators, mucolytics, or expectorants were administered as per usual

physician practice in each treatment group. The study was approved by each investigator's institutional review board and all patients gave written informed consent prior to enrollment.

STUDY DRUGS AND LABORATORY ASSESSMENTS

Patients were randomized in blinded fashion at the first visit in a 1:1:1 ratio to moxifloxacin 400 mg once daily for 5 days, moxifloxacin 400 mg once daily for 10 days, or clarithromycin 500 mg bid for 10 days based on a randomization code that was computer generated by the Bayer Corporation. Following random assignment to treatment, patients took two encapsulated tablets twice daily at approximately the same time of day with 120 ml (4 oz) of water, with or without food. Patients were randomized to either oral moxifloxacin 400 mg administered once daily for either 5 or 10 days or clarithromycin 500 mg bid for 10 days. For the purpose of study blinding, the patients taking moxifloxacin received placebo to maintain uniform dosing. All drugs were encapsulated in opaque gelatin capsules for blinding purposes. At the end of therapy, each patient was questioned regarding the number of capsules taken during the study in order to document patient compliance.

Standardized clinical assessment and bacteriological evaluation (Gram stain and sputum culture) were performed pre-therapy, during therapy (days 3–5), at the end of therapy visit (post-therapy days 0–6) and at the follow-up visit (post-therapy days 7–17). Disk diffusion and broth microdilution susceptibility testing were performed according to NCCLS guidelines (20,21). *Haemophilus* spp. and *M. catarrhalis* also were tested for β-lactamase production. *S. pneumoniae* was tested for penicillin susceptibility, either by oxacillin disk or by penicillin Etest strip. ECGs were performed prior to initiation of study drug therapy and once during therapy on days 3–5.

Two populations were evaluated in this trial: patients with a pretherapy pathogen for whom drug efficacy could be evaluated (efficacy-valid population; see below) and all randomized patients who received study drug (intent-to-treat population) for drug safety evaluation.

EFFICACY/SAFETY MEASUREMENTS

The objective of this study was to demonstrate equivalence of the three treatment regimens with respect to bacteriological and clinical responses. The end points were bacteriological and clinical response at the end of therapy (post-therapy days 0–6) and at follow-up (7–17 days post-therapy), as well as overall response (defined below) for those patients with a pretherapy pathogen.

For a course of therapy to be judged valid for efficacy (i.e. efficacy valid population), the following criteria were met: ABECB confirmed both by appropriate history of underlying disease and presentation with symptoms of acute infection; pneumonia excluded radiologically; pretherapy organism isolated and identified from pretherapy sputum culture; study drug given for at least 48 h if a clinical failure, or for at least 5 days if a clinical success; no concurrent administration of non-study antimicrobial agents, unless the patient was a treatment failure or relapse; and at least 80% compliance with study drug regimen.

Clinical response was based on serial examinations of the patient using the following parameters: objective signs of auscultatory findings (rales, rhonchi, wheezing, breath sounds); prolongation of expiratory phase; presence of fever $>38^{\circ}$C; and presence of WBC $>12\,000$ cells mm^{-3}; and subjective symptoms of chest pain or discomfort; change in cough frequency and severity; sputum characteristics (thickness and volume); and dyspnea. At the end of therapy, clinical response was graded as 'clinical cure' [disappearance of acute signs and symptoms related to the infection (complete return to a stable pre-exacerbation condition) or sufficient improvement such that additional or alternative antimicrobial therapy was not required], 'clinical failure' (insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy was required), or 'indeterminate' (clinical assessment was not possible to determine for any reason). The clinical response at the follow-up visit was reported as: 'continued clinical cure' (disappearance of acute signs and symptoms of infection or continued improvement where additional or alternative antimicrobial therapy was not required), 'clinical recurrence' [reappearance of signs and symptoms of an acute exacerbation of bronchitis considered related to an infectious (bacterial) process such that reinstitution of antimicrobial therapy was required], or 'indeterminate' (patients in whom a clinical assessment was not possible to determine). Overall clinical response was also determined based on a summation of end of therapy and follow-up visit evaluations. Overall clinical resolution occurred if the patient's end of therapy response was resolution or indeterminate with a follow-up evaluation of continued resolution. Overall clinical failure was considered in patients with either an end of therapy evaluation of failure or a follow-up evaluation of recurrence.

Bacteriological response was based on the results of cultures taken before and after therapy. At the end of therapy, the bacteriological responses were graded as eradication, presumed eradication (if no material was available due to a clinical success), persistence, persumed persistence (no material was available in a patient considered a clinical failure), or indeterminate (if bacteriological response to the study drug was not evaluable for any reason). In addition, superinfection was defined as isolation of a new pathogen in a symptomatic patient. For patients with an end of therapy response of eradication or presumed eradication, follow-up bacteriological eradication was defined as: continued eradication, continued presumed eradication, relapse (original causative organism present), reinfection (new causative organism identified) and indeterminate (not evaluable for any reason).

All patients receiving at least one dose of study drug were evaluable for safety (intent-to-treat population). Safety was evaluated on the basis of physical examination findings, ECGs, adverse events, intercurrent illness and laboratory

tests, including routine hematology, blood chemistry and urinalysis tests. Investigators rated each adverse event subjectively according to relationship to study drug (probable, possible, remote, or none) and severity (mild, moderate, severe, or serious or life threatening).

STATISTICAL ANALYSES

The primary goal of the study was to determine whether moxifloxacin, given for 5 days or for 10 days, was equivalent to clarithromycin in patients with ABECB. *A priori* ordered hypotheses were constructed and a sequentially rejective multiple test procedure was planned. If a test of non-equivalence of 10-day moxifloxacin *vs.* clarithromycin was rejected, then a test of the 5-day regimen would be performed. This multiple test procedure would keep the overall significance level at alpha=0.05 for two-sided tests of the primary efficacy variable.

For each evaluation of clinical and bacteriological response, a two-sided 95% confidence interval for the weighted difference between treatment groups was constructed using Mantel–Haenszel weights (weighting by center). Equivalence was defined as the lower limit of the two-sided 95% confidence interval for the difference between groups being greater than −15%. With the sample size of 420 efficacy-valid patients enrolled, the study had a power of 90% to test the null hypothesis of inequivalence, assuming a failure rate of 15% for each treatment group.

For categorical variables, a chi-squared test was used to test for the differences between groups. For continuous variables, a one-way analysis of variance was used, with a term included for treatment. Comparisons of the incidence rates of adverse events between the three study drug groups were done descriptively. Events were tabulated by type (according to the COSTART glossary) and frequency for all adverse events and for those events considered to be related to drug treatment.

Results

Of the 936 patients enrolled, 491 (52%) had a pathogen isolated pretherapy. Nine hundred and twenty-six (99%) patients comprised the intent-to-treat population. Ten patients were excluded from the intent-to-treat analysis because they were lost to follow up after the initial visit. Eight hundred and thirty-seven patients completed the study (284 in the 5-day moxifloxacin group, 277 in the 10-day moxifloxacin group and 276 in the clarithromycin group). Among 99 patients who failed to receive a full course of study drug, adverse events were the main reason for premature discontinuation of treatment across the regimens (47%; see safety section below). Four hundred and twenty patients with a pretherapy organism were valid for the efficacy analysis (143 5-day moxifloxacin group, 148 10-day moxifloxacin group and 129 clarithromycin). The most common reasons for exclusion from the efficacy analysis were: no pretherapy organisms (n=337), essential data missing or invalid (n=44), violating of inclusion/exclusion criteria (n=44), insufficient duration of therapy (n=29), lost to follow up (n=29), or non-compliance with study drug (n=29).

As shown in Table 1, the three treatment groups who comprised the efficacy-valid population were well matched with regard to age, gender, ethnic origin, smoking history and infection type. The majority of patients enrolled were males (mean age, 55 years) and patients experienced an average of 2·6 treated AECBs during the past year. Ninety percent had a history of present or past smoking (mean 32 yr). Over 75% of efficacy-valid patients presented with Type 1 infections (Table 1). Baseline demographic and clinical characteristics of the intent-to-treat group were similar to those considered to be efficacy-valid, with the exception of the average number of cigarettes smoked (P=0·036). Patients in the two moxifloxacin groups averaged between two and three more cigarettes per day than those in the clarithromycin group.

CLINICAL RESPONSE

Table 2 illustrates the clinical and bacteriological success rates for the three populations of patients analyzed at the various timepoints assessed during the study. The overall clinical response rates for the efficacy-valid group were 89% for the 5-day moxifloxacin and 91% for the clarithromycin regimens (95% CI=−8·7%, 4·2%). For the 10-day moxifloxacin group, the overall clinical response rate was 91% (95% CI for 10-day moxifloxacin minus clarithromycin=−5·9%, 6·8%). Thus, both moxifloxacin regimens were found to be statistically equivalent to the clarithromycin regimen. Furthermore, baseline demographic characteristics did not appear to influence the success rates for the treatment groups.

For the efficacy-valid group, 16 (9%) of the 5-day moxifloxacin, 14 (11%) of the 10-day moxifloxacin and 11 (9%) of the clarithromycin recipients were determined to be clinical failures. Overall clinical failure was associated with bacteriological persistence or recurrence for five (3%) 5-day moxifloxacin, six (4%) 10-day moxifloxacin and five (4%) clarithromycin-treated patients.

BACTERIOLOGICAL RESPONSE

The overall bacteriological response rates by patient for the efficacy-valid group were 89% (127/143) for the 5-day moxifloxacin and 85% (110/129) for the clarithromycin regimens (95% CI=−3·7%, 10·5%) (see Table 2). For the 10-day moxifloxacin group, the overall bacteriological response rate was 91% (135/148; 95% CI for 10-day moxifloxacin minus clarithromycin=0·3%, 14·5%). Thus, both moxifloxacin regimens were found to be statistically equivalent to the clarithromycin regimen with respect to bacteriological response. Overall organism eradication rates, including presumed eradication, at the end of therapy were 94% (127 of 135) for 5-day moxifloxacin, 95% (138 of 145) for 10-day moxifloxacin and 91% (115 of 127) for clarithromycin therapy. Corresponding rates at the 7–17 day post-therapy follow-up visit were 89% (127 of 143), 91% (135 of 148) and 85% (110 of 129), respectively.

TABLE 1. Demographics and baseline medical characteristics

Variable	Intent-to-treat population			Efficacy-valid population		
	5-day Moxifloxacin (*n*=312)	10-day Moxifloxacin (*n*=302)	10-day Clarithromycin (*n*=312)	5-day Moxifloxacin (*n*=143)	10-day Moxifloxacin (*n*=148)	10-day Clarithromycin (*n*=129)
Age, years						
Mean ± SD	56·9 ± 15·4	56·2 ± 15·8	55·5 ± 16·0	56·6 ± 15·5	55·0 ± 16·1	54·2 ± 15·9
Range	19–89	18–88	18–90	21–89	23–84	19–87
Sex, *n* (%) male	169 (54)	160 (53)	158 (51)	87 (61)	78 (53)	78 (60)
Race, *n* (%) Caucasian	237 (76)	228 (75)	229 (73)	97 (68)	99 (67)	78 (60)
Type of AECB infection per Anthonisen (5), *n* (%)						
I	239 (77)	231 (76)	247 (79)	109 (74)	109 (74)	106 (82)
II	69 (22)	65 (22)	59 (19)	33 (23)	38 (26)	21 (16)
III	4 (1)	6 (2)	6 (2)	1 (<1)	1 (<1)	2 (2)
Mean number (%) of exacerbations in past 12 months	2·7	2·7	2·7	2·7	2·6	2·5
Concomitant systemic steroid therapy, *n* (%)	75 (24)	59 (20)	74 (24)	32 (22)	26 (18)	25 (19)
History of cigarette smoking, past or present						
n (%)	269 (86)	252 (83)	127 (89)	275 (88)	129 (87)	118 (91)
Length of history (yrs)	32·5	33·7	32·4	27·3	28·9	27·2
Average number cigarettes smoked per day						
n	267	250	273	126	128	118
Mean	26·7	27·5	24·5	27·3	28·9	27·2

*includes patients who had pretherapy pathogen.

TABLE 1A. Pre-therapy signs and symptoms

	5-day Moxifloxacin N=143 *n*/N (%)	10-day Moxifloxacin N=148 *n*/N (%)	Clarithromycin N=129 *n*/N (%)
Presence of wheezes	92 (64)	106 (72)	88 (68)
Rales	35 (25)	28 (19)	29 (23)
Rhonchi	99 (69)	115 (78)	97 (75)
Expiration prolonged	80 (56)	94 (64)	72 (56)
Decreased breath sounds	51 (36)	55 (37)	53 (41)
Patients with symptoms increased from baseline*			
Sputum volume	141 (99)	142 (96)	124 (96)
Sputum purulence /thickness	143 (100)	148 (100)	128 (99)
Cough frequency	141 (99)	145 (98)	127 (98)
Chest discomfort	82 (57)	70 (47)	74 (57)
Dyspnea	110 (77)	114 (77)	110 (85)

*Baseline=status between exacerbations

The pretherapy organisms identified in those patients who were clinical failures were as follows for 5-day moxifloxacin: *S. aureus*—1, *K. pneumoniae*—2, *E. cloacae*—1, *P. auruginosa*—4, *M. catarrhalis*—5, *H. influenzae*—4; for 10-day moxifloxacin: *S. aureus*—2, *Streptococcus* Sp.—1, *S. pneumoniae*—2, *E. coli*—1, *E. aerogenes*—1, *S. marcescens*—1, *C. freundii*—1, *P. auruginosa*—4, *M. catarrhalis*—2, *H. influenzae*—3; and for 10-day clarithromycin: *S.*

TABLE 2. Clinical and bacteriological success rates

	5-day Moxifloxacin *n*/N (%)	10-day Moxifloxacin *n*/N (%)	Clarithromycin *n*/N (%)
Efficacy-valid patients			
Clinical Success			
End of therapy (0–6 days post-therapy)	127/135 (94)	136/144 (94)	121/127 (95)
Follow-up (7–17 days post-therapy)	127/135 (94)	134/140 (96)	118/123 (96)
Overall*	127/143 (89)	134/148 (91)	118/129 (91)
Bacteriological Success			
End of therapy (0–6 days post-therapy)	127/135 (94)	138/145 (95)	115/127 (91)
Follow-up (7–17 days post-therapy)	127/143 (89)	135/148 (91)	110/129 (85)
Intent-to-treat patients			
Clinical Success			
End of therapy (0–6 days post-therapy)	274/288 (95)	266/281 (95)	268/286 (94)
Follow-up (7–17 days post-therapy)	242/256 (94)	250/258 (97)	232/245 (95)
Overall*	242/270 (90)	250/273 (92)	232/263 (88)
Bacteriological Success			
End of therapy (0–6 days post-therapy)	142/152 (93)	156/165 (95)	130/144 (90)
Follow-up (7–17 days post-therapy)	130/149 (87)	144/159 (91)	113/136 (83)

*Overall response includes failures occurring at end of therapy which are carried forward in addition to clinical evaluations at the follow-up timepoint. Indeterminates were excluded from the denominator at the end of therapy timepoint. The difference between the overall denominator and the end of therapy denominator represents the number of indeterminates at end of therapy.

aureus—2, *S. pneumoniae*—3, *N. meningitidis*—1, *P. mirabilis*—1, *P. auruginosa*—1, *H. influenzae*—5 and *K. pneumoniae*—1.

There were 12 superinfections in total, five among the efficacy-valid patients (three of the 5-day moxifloxacin-treated patients and two of the clarithromycin-treated patients). In addition, among the total patient population, four patients in the 5-day moxifloxacin group, one patient in the 10-day moxifloxacin and seven patients in the clarithromycin group who had negative cultures initially and positive cultures at the follow-up visit. Reinfections or recurrences were reported for seven and ten patients in the 5-day and 10-day moxifloxacin, respectively, compared to 10 clarithromycin recipients. Three of the four 5-day moxifloxacin superinfections and three of the six 10-day moxifloxacin reinfections were due to *S. pneumoniae*. *H. influenzae* or *H. parainfluenzae* accounted for four of the seven clarithromycin superinfections and two of the five clarithromycin recurrences.

Five hundred and twenty-nine pathogens were isolated pretherapy from 420 efficacy-valid patients. *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* were isolated from 21%, 16% and 11% of efficacy-valid patients at study entry. *H. parainfluenzae*, *S. aureus* and *K. pneumoniae* were isolated from 9%, 8% and 9% of efficacy-valid patients at study entry. Among 110 *H. influenzae* isolates, nine produced beta-lactamase and of 60 pneumococcal isolates, five were found to be penicillin-resistant based on MIC data. Among 85 *M. catarrhalis* isolates, 56 produced beta-lactamase.

Based on our definition of bacteriological response, bacteriological eradication for *H. influenzae* was reported for 89%, 97% and 76% of isolates in the 5-day moxifloxacin, 10-day moxifloxacin and clarithromycin regimens, respectively. Corresponding rates of eradication for *M. catarrhalis* were 85%, 96% and 100%. For *S. pneumoniae*, 5-day and 10-day moxifloxacin regimens eradicated 100% and 95% of organisms compared to 91% in the clarithromycin group. One hundred percent of *H. parainfluenzae* isolates were eradicated by all three treatment regimens. The individual eradication rates at the end of study and end of therapy are shown in Table 3.

SAFETY

The safety population comprised 926 patients (312 5-day moxifloxacin, 302 10-day moxifloxacin and 312 clarithromycin). Clarithromycin-treated patients reported slightly more treatment-emergent events (48%) then the 5-day moxifloxacin (42%) or 10-day moxifloxacin (46%) groups. Forty-seven (5%) patients (4% 5-day moxifloxacin, 4% 10-day moxifloxacin and 7% clarithromycin) were prematurely discontinued from the study due to 95 adverse events. In both moxifloxacin groups, gastrointestinal events (n=16) were the most frequent reason for early discontinuation of study drug. Similarly, for clarithromycin recipients, gastrointestinal-related adverse were most often reported (n=12).

Drug-related events were reported by 26% of 5-day moxifloxacin, 30% of 10-day moxifloxacin and 33% of clarithromycin-treated patients. Events occuring in at least 2% of the study population and considered to be drug-related are summarized in Table 4. Among these patients,

TABLE 3. Eradication rates for the most common pre-treatment organisms isolated

	5-day Moxifloxacin *n*/N (%)	10-day Moxifloxacin *n*/N (%)	Clarithromycin *n*/N (%)
End of therapy (0–6 days post-therapy)			
Haemophilus influenzae	37/37 (100)	32/32 (100)	33/40 (83)
Moraxella catarrhalis	32/33 (97)	25/25 (100)	24/24 (100)
Streptococcus pneumoniae	15/15 (100)	21/21 (100)	21/23 (91)
Staphylococcus aureus	14/14 (100)	15/15 (100)	8/8 (100)
Klebsiella pneumoniae	18/20 (90)	14/14 (100)	11/11 (100)
Haemophilus parainfluenzae	14/14 (100)	17/17 (100)	14/14 (100)
Follow-up (7–17 days post therapy)			
Haemophilus influenzae	33/37 (89)	31/32 (97)	31/41 (76)
Moraxella catarrhalis	29/34 (85)	26/27 (96)	24/24 (100)
Streptococcus pneumoniae	16/16 (100)	20/21 (95)	21/23 (91)
Staphylococcus aureus	15/16 (94)	17/18 (94)	7/8 (88)
Klebsiella pneumoniae	17/20 (85)	14/15 (93)	10/11 (91)
Haemophilus parainfluenzae	16/16 (100)	21/21 (100)	14/14 (100)

TABLE 4. Drug-related adverse occurring in at least 2% of patients

Adverse Event	5-day Moxifloxacin *n* (%) *n*=312	10-day Moxifloxacin *n* (%) *n*=302	Clarithromycin *n* (%) *n*=312
Headache	7 (2%)	7 (2%)	2 (<1%)
Asthenia	2 (<1%)	5 (2%)	3 (<1%)
Nausea	12 (4%)	23 (8%)	23 (7%)
Diarrhea	15 (5%)	18 (6%)	15 (5%)
Vomiting	3 (<1%)	8 (3%)	9 (3%)
Dyspepsia	7 (2%)	2 (<1%)	2 (<1%)
Flatulence	4 (1%)	2 (<1%)	5 (2%)
Dizziness	9 (3%)	14 (5%)	4 (1%)
Nervousness	2 (<1%)	4 (1%)	5 (2%)
Pruritus	3 (<1%)	2 (<1%)	5 (2%)
Taste perversion	6 (2%)	6 (2%)	26 (8%)

gastrointestinal events were the most common drug-related adverse events reported across all three treatment regimens. Nausea and vomiting occurred in similar, but higher, rates in those given 10-day moxifloxacin or clarithromycin compared to 5-day moxifloxacin recipients. Dizziness was more often reported in moxifloxacin-treated patients, whereas taste perversion occurred at a four-fold higher rate in clarithromycin-treated patients.

Thirty-nine (4%) patients in the safety population were hospitalized during the study (3% of 5-day moxifloxacin, 4% of 10-day moxifloxacin, 5% of clarithromycin). Forty-six patients had at least one event that was considered serious or life threatening (13 5-day moxifloxacin, 15 10-day moxifloxacin and 18 clarithromycin). For all three regimens, most of the hospitalizations or serious adverse events were the result of exacerbations of underlying disease and were considered unrelated to study drug administration. Two deaths occurred during the study period—one 5-day moxifloxacin and one clarithromycin-treated patient. Neither death occurred while the patient was receiving the study drug and neither death was categorized by the investigator as being drug-related. The patient on moxifloxacin died from pancreatitis and the clarithromycin treated patient died from a presumed myocardial infarction.

Discussion

AECB is a relatively common condition and bacterial infection accounts for at least 50% of all episodes. However, few well designed trials have been conducted to ascertain optimal antimicrobial therapy in AECB due to proven bacterial etiology (5). Furthermore, the selection of

an ideal agent for ABECB has become more difficult due to the increasing levels of respiratory tract pathogens that are β-lactam and macrolide-resistant (10,12). Although the empiric use of antimicrobial treatment for AECB has been debated, certain high risk groups deserve prompt initiation of therapy (e.g. those with increasing purulence, dyspnea and a likely bacterial etiology and patients requiring hospitalization (9).

One major flaw of many previously conducted trials has been the attempt to determine the efficacy of anti-microbials in populations of mixed etiologies, that is, populations that include those whose exacerbations are of non-bacterial origin. This practice dilutes any real effect of the anti-microbial and this is further confused if the underlying lung disease is poorly defined. In order to truly assess the benefit of an antimicrobial for the treatment of ABECB, the patient population should have a documented bacterial infection by Gram stain criteria (6). Although empiric therapy is unlikely to be discouraged, it is important to obtain data on both bacteriological and clinical efficacy as it is only those patients with bacterial exacerbations who will benefit from antibiotic therapy. Then there can be some assurance that if a physician does treat empirically for AECB of unspecified etiology, the bacterial exacerbations will be treated appropriately.

To address some of these concerns, but still conform to the infectious Diseases Society of America's clinical trial recommendations for treatment of AECB (23), we predominantly recruited patients with Type I AECB (75%) because it is this category of patients who have been shown to be most likely to benefit from antimicrobial therapy (7). It should be noted, however, that since only 52% of enrolled subjects had a bacterial pathogen, these symptoms alone are not diagnostic for bacterial infection.

We found that the overall clinical response at 7–17 days post therapy for efficacy-valid patients with a pretherapy pathogen ranged from 89% to 91% for the three regimens studied. These rates are generally consistent with the rates observed in previous fluoroquinolone (24–29) and clarithromycin (28–32) studies, although it should be noted that in some of these studies the efficacy valid population was not limited to those patients with a pretherapy pathogen.

Because most physicians do not routinely obtain sputum specimens for bacteriological studies (e.g. Gram stain, etc.) it is essential that results in real ABECB demonstrate substantial efficacy. With such evidence, the risk of treating non-bacterial exacerbations is then limited to the incidence of adverse events. Physicians should consider the risk of exposing patients with non-ABECB to potential adverse events without any benefit. In this study, the most common adverse events for both moxifloxacin and clarithromycin were gastrointestinal. In general, both study drugs were well tolerated. Drug-related adverse events were reported at comparable rates across the three treatment groups (26% 5-day moxifloxacin, 30% 10-day moxifloxacin, 33% clarithromycin); although, the rate of treatment withdrawals due to adverse events for the clarithromycin-treated group was somewhat higher than that for the two moxifloxacin treated groups (7% clarithromycin *vs.* 4% 5-day moxifloxacin and 4% 10-day moxifloxacin).

One limitation of the current trial is the lack of information on long-term relapse rates. While short-term relapse rates were low following all three treatment regimens (4%), continued follow-up for greater than 31 days was not required as part of this registration trial. Determination of the infection-free interval (i.e. time from end of one exacerbation to the beginning of the next exacerbation) is a valuable tool for defining important differences in antimicrobial regimens (5), and further studies should be considered to accurately determine the infection-free interval for moxifloxacin, comparing 5 and 10 day courses. Clarithromycin, which demonstrates a reasonable short-term response rate, has been shown to have a relatively short infection-free interval (28). In the future, studies should be designed to evaluate if shortening the course of therapy would affect the infection-free interval.

The optimal duration of antimicrobial therapy for ABECB is unknown, although the administration of at least 10–14 days of therapy has been recommended (4,5). Levofloxacin, grepafloxacin and trovafloxacin have each been evaluated in regimens as short as 7–10 days with acceptable rates of early clinical success ($>90\%$) (33–36). Another recent study has demonstrated the effectiveness of short course therapy for AECB with clinical success rates comparable to those achieved here. In that study, a 3-day course of azithromycin was clinically and microbiologically equivalent to 10-day amoxicillin clavulanate in patients with Type I ABECB (37). The validity of the conclusions from these studies (33–37) however is questionable, given that none compared short-course to long or conventional course treatment schedules using pathogen-positive acute bacterial exacerbations and all were designed to show equivalence to comparator agents. Investigations to determine which categories of chronic bronchitis patients could be appropriate for short-course treatment would be required to clarify this issue. Short-course treatment regimens may improve patient compliance, reduce the risk of adverse events, provide potential cost savings and possibly reduce the pressures that drive antibiotic resistance (38). Our data support the use of both 5-day and 10-day moxifloxacin for the treatment of ABECB; clinical and bacteriological success rates approached 90% following this regimen. Moreover, because the 5-day and 10-day moxifloxacin regimens were clinically and bacteriologically equivalent to 10-day clarithromycin, 5-day moxifloxacin may be a preferred regimen for some patients. Nonetheless, surveillance of resistance patterns must be ongoing in order to assist physicians in prescribing the most appropriate antimicrobial.

Ideal antibiotic therapy for ABECB should rapidly resolve the infection and eradicate the most commonly isolated respiratory pathogens. As expected *H. influenzae* followed by *M. catarrhalis* and *S. pneumoniae* were the most frequently isolated organisms from our efficacy-valid population. The numbers of each specific type of bacteria were too small to detect statistically significant differences in bacteriological outcome across the three treatment groups. Although not a statistically significant result, it is worth noting that both moxifloxacin regimens had higher

eradication rates against *H. influenzae* compared to clarithromycin. Clarithromycin's relatively poor ability to eradicate *H. influenzae* has been reported previously (28).

In summary, this trial has demonstrated that patients with ABECB can be as safely and effectively treated with 5 or 10 days of moxifloxacin as compared to a standard course of clarithromycin. The shorter course moxifloxacin may prove to be a convenient once-daily treatment regimen for this patient population.

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